Diagnostic challenges in osteoporosis

Indications for bone densitometry and establishing secondary causes

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abstract

OBJECTIVE To review indications for assessing bone mineral density (BMD) and to review patient characteristics and diseases associated with osteoporosis.

QUALITY OF EVIDENCE This paper is based on data from longitudinal observational studies of how BMD and other risk factors affect development of fragility fractures and on several peer-reviewed publications describing pathophysiology of bone turnover and pathogenesis of osteoporosis. Indications for obtaining BMD and monitoring treatment are based on the recommendations of the Osteoporosis Society of Canada derived from the consensus opinion of a panel of experts in osteoporosis and based on their review of the primary literature.

MAIN MESSAGE Measurement of BMD provides the best single objective predictor of the relative risk of fracture at sites such as the vertebrae, hip, and wrist, predicting the likelihood of fracture with as much accuracy as measurement of elevated blood pressure predicts stroke. In addition to making the diagnosis of osteoporosis, BMD measurements are used to monitor progression of osteoporosis and effects of therapy. At this date, dual energy x-ray absorptiometry is preferred for measuring BMD. The most likely causes of osteoporosis in any patient are age, hormone withdrawal (in both men and women), and drugs (particularly corticosteroids). Secondary causes, particularly hyperparathyroidism and multiple myeloma, should be excluded by performing appropriate laboratory tests.

CONCLUSION A BMD measurement should be obtained for patients at high risk of osteoporosis and fragility fractures to guide initiation and monitor success of therapy.

résumé

OBJECTIF Passer en revue les cas où il est indiqué de procéder à une évaluation du contenu minéral osseux (CMO) ainsi que les caractéristiques des patients et des maladies associées à l'ostéoporose.

QUALITÉ DES DONNÉES Le présent article se fonde sur des données tirées d'études d'observation longitudinales sur l'influence que le CMO et d'autres facteurs de risque exercent sur le développement de fractures de fragilité et sur plusieurs publications évaluées par les pairs décrivant la pathophysiologie du renouvellement osseux et la pathogénie de l'ostéoporose. Les cas où il est indiqué de procéder à une mesure du CMO et à la surveillance de la thérapie sont définis en fonction des recommandations de la Société de l'ostéoporose du Canada. Ces dernières sont tirées d'opinions consensuelles d'un groupe d'experts en ostéoporose basées sur une étude des ouvrages scientifiques spécialisés.

PRINCIPAL MESSAGE La mesure du CMO constitue le meilleur et le seul prédicteur objectif du risque relatif de fracture à des endroits comme les vertèbres, les hanches, les poignets. Sa précision dans la prédiction de la probabilité de fracture se rapproche de celle de la mesure de l'hypertension comme prédicteur d'accidents vasculaires cérébraux. En plus de servir au diagnostic, les mesures du CMO servent aussi à surveiller la progression de l'ostéoporose et les effets de la thérapie. À l'heure actuelle, l'absorptiométrie à rayons X en double énergie est la méthode privilégiée pour mesurer le CMO. Les causes les plus probables de l'ostéoporose chez les patients se situent dans l'âge, la baisse du taux d'hormones (chez l'homme et chez la femme) et les médicaments (en particulier les corticostéroïdes). Les causes secondaires, en particulier l'hyperparathyroïdie et les myélomes multiples, doivent être exclues au moyen d'épreuves appropriées en laboratoire.

CONCLUSION Il faut obtenir une mesure du CMO chez les patients à risque élevé de souffrir d'ostéoporose et de fractures de fragilité pour déterminer s'il faut initier une thérapie et en suivre la réussite.

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Albright et al[1,2] described osteoporosis well over half a century ago and noted its major consequence, predisposition to skeletal fractures. In large part because of an aging population, fracture of osteoporotic bones has become an important public health problem whether measured in dollars (costs estimated at about $1.3 billion yearly in Canada) or in human costs of decreased quality of life and increased mortality.[3]

For years, the lack of reliable methods for early and accurate diagnosis of osteoporosis and a paucity of treatments hampered attempts at reducing its adverse affects. As we enter the 21st century, however, we have developed the technology and drugs for estimating fracture risk and decreasing the likelihood of fracture in individuals. Because family physicians are usually the first to see patients at risk of osteoporosis, they are challenged to use these new methods for early detection of osteoporosis to improve the "bone outcome" of their patients. In this article I discuss indications for measuring bone mineral density (BMD), how to interpret those measurements, how to monitor osteoporosis therapy, and how to evaluate patients to rule out secondary causes of osteoporosis.

Quality of evidence

A MEDLINE search (January 1980 to July 2000, inclusive) was performed using the correlative terms osteoporosis, risk factors, and bone mineral density to identify articles evaluating the clinical and laboratory factors associated with osteoporosis and predicting occurrence of fragility fractures. Articles cited in the bibliography are primary references on the pathophysiology and pathogenesis of bone turnover and fractures. These observational studies were selected because they were prospective, longitudinal, long-term studies of large sample size (hundreds to thousands) using multivariate and regression analyses to ascertain risks for development of osteoporosis and fractures. The conclusions of the studies are somewhat limited by their relative restriction to white women.

Recommendations of the Osteoporosis Society of Canada (OSC) are based on a consensus of opinion of a panel of medical experts after a literature review, but are not derived from formal evidence-based methods. Such an exercise is currently in progress. The overall quality of the data on which this article is based is judged as very good.

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Why measure BMD?

The slow, progressive development of osteoporosis is painless; if there were no clinical consequences, there would be no need to diagnose the condition. Osteoporosis is notable for both decreased bone quantity and lower bone quality. Both features lead to increased bone fragility and classic low-trauma fractures of the vertebrae, wrists, and hips.[4] Before a fracture occurs, patients' clinical features cannot reliably predict their bone mass or fracture risk.[5,6]

In contrast, measurement of BMD is central to diagnosis of osteoporosis, as BMD measurement is the single best predictor of fracture risk in repeated prospective assessments.[7-11] Indeed, BMD measurement estimates about 60% to 70% of a patient's total risk for fracture.[12] The BMD measurement predicts risk of fracture as accurately as measurement of elevated blood pressure predicts risk of stroke and more accurately than measurement of cholesterol predicts risk of heart disease.[13,14]

While BMD measurement provides the most important objective information of fracture risk, inclusion of additional clinical factors more comprehensively assesses total risk[15] (**Table 1**[3]). Some terms,

Table 1. Risk factors for osteoporosis

RISK FACTORS FOR DECREASED BONE MASS
Advanced age (ie, older than 70 years)
Female sex
White or Asian race
Low body weight
Late menarche, early menopause
Estrogen deficiency
Low exposure to sunlight
Positive family history
Lifestyle (eg, inadequate calcium intake, cigarette smoking, lack of physical activity, excessive alcohol intake)
RISK FACTORS FOR FRACTURE INDEPENDENT OF AGE AND BONE MINERAL DENSITY
Poor bone quality (eg, history of previous fracture)
Family history of fracture
Hip geometry for hip fractures (eg, increased hip axis length: distance between greater trochanter and inner pelvic rim)
Propensity for falls (eg, poor visual acuity, neuromuscular impairment, postural instability, lower limb weakness, treatment with drugs affecting blood pressure, psychotropic drugs)

Adapted from Josse et al.[3]

such as older age at menarche, early menopause, or excessive alcohol intake, are inexact and are best interpreted by comparison to people with no such risk factors. Daily drinking of alcohol can affect bone metabolism, while social drinking does not. Hip geometry is an example of a risk factor independent of BMD, but it is not useful for clinical practice.

Definition of osteoporosis

A World Health Organization (WHO) expert panel has used BMD to define osteoporosis (**Table 2**). The BMD is expressed as a T-score representing the number of standard deviations (SD) away from a mean BMD score derived from a panel of young normal subjects of the same sex, roughly between the ages of 20 and 35, who are at peak bone density. The more negative the score, the lower the bone mass and the greater the risk of fracture. Still, the BMD provides a relative and not an absolute measure of risk for a fracture. Each SD decrease in BMD score represents about a 12% reduction in bone, and risk of fracture approximately doubles for every SD decrease.[4] Thus risk is increased even at scores not considered diagnostic of osteoporosis.

Other factors augment fracture risk, such as qualitative abnormalities of bone and increased rates of bone turnover that are not reflected in the simple measurement of bone mass (**Table 1**[3]). Thus, at the same BMD, patients with family or personal histories of fragility fractures and older patients are at greater risk of fracture than people without such features. The BMD is measured at multiple locations at the hip and lumbar vertebrae, and the worst results are used to define the status of the bones and assess risk of fracture. In older patients, hip BMD is often more reliable than spinal BMD because osteoarthritis of the lumbar spine falsely elevates the BMD. With or without concomitant osteoarthritis, a low spinal BMD score is predictive of fracture risk.

Table 2. World Health Organization definition of osteoporosis in postmenopausal women

Normal: BMD < 1 SD below young adult mean,
T-score better than –1

Osteopenia: BMD > 1 SD but < 2.5 SD below mean,
T-score between –1 and –2.5

Osteoporosis: BMD > 2.5 SD below mean,
T-score worse than –2.5

Severe osteoporosis:
Osteoporosis *plus* one or more fragility fractures

Many laboratories also provide Z-scores comparing a patient's BMD to her age-matched peers. This measurement's utility is disputed because T-scores are used to define osteoporosis and to guide therapy. It can be argued that a very negative Z-score, indicating that a person's bone is much more fragile than her peers, might increase awareness of the need for therapy or suggest the presence of a secondary process requiring additional evaluation, such as hyperparathyroidism. For patients younger than 30 (before peak bone mass has been achieved), Z-scores are the only way of ascertaining the status of bone mass in comparison to age-matched controls.

Indications for performing BMD measurement

Many precedents for screening the population to detect disease or risk factors exist, for example, hypertension, diabetes, hyperlipidemia, breast cancer, and cervical cancer. Osteoporosis is no different from these conditions. It is a high-prevalence disease associated with high monetary and human costs; it can be detected early; effective treatment is available, and therapy should reduce future adverse consequences.

Access to measurement of BMD is not uniform across Canada and the United States, however, and policy often appears guided by considerations of the costs of diagnosis and therapy. Attempts to demonstrate a favourable cost-benefit ratio[4] are highly complex and require estimates of potential costs during a possible 25- to 50-year period for affected people. There is ongoing debate over age of first screening and frequency of screening. In large part because of the controversy, the case for selective screening (as opposed to mass screening) has been advanced by advocate groups, such as the OSC and the National Osteoporosis Foundation in the United States, as a means of identifying segments of the population at greater risk of fracture and of establishing precedents for reimbursement.

The OSC recommendations (**Table 3**[3]) for baseline screening are like many other published guidelines. They suggest measuring BMD if a patient is willing to take therapy. They recognize that the largest segment of the population at risk of osteoporosis is estrogen-deficient (white) women who sustain rates of bone loss of about 2% a year and in whom the lifetime risk of hip, wrist, or vertebral fracture is about 40%.[4] In men the risk is around 13%.[4] Several additional clinical factors increase risk of fracture at any specific BMD measurement, such as a personal or family history of osteoporotic fractures, weight below 57 kg, and height greater than 168 cm (5'7"). The recommendations outline drugs (steroids, phenytoin, and other anticonvulsants, prolonged

Table 3. Indications for measurement of BMD:
Position statement of the Osteoporosis Society of Canada

It is reasonable to measure BMD when the result would affect clinical decision making. Measurement of baseline BMD in postmenopausal women is suggested if any of the following major risk factors are present:

- premature menopause (younger than 45 years) or long-standing premenopausal hypogonadism
- glucocorticoid therapy (7.5 mg or more daily of prednisone or equivalent) for longer than 3 months or Cushing syndrome
- family history of osteoporosis (in first-degree relatives)
- previous fragility fracture (minimal trauma)
- long-standing malabsorption or malnutrition
- long-standing use of anticonvulsants
- primary hyperparathyroidism
- chemotherapy exposure (assuming long-term survival is expected)
- low body weight (BMI less than 20) or weight below 57 kg (125 lb)
- postmenopausal with two or more of the following risk factors: smoking, excessive alcohol intake, low calcium intake, hyperthyroidism

These recommendations are for postmenopausal women but for the most part apply equally to men who have hypogonadism. In Ontario in 1999, the provincial health plan (OHIP) divided patients into high-risk and low-risk categories. High-risk patients include people with any major risk factor and have insured unrestricted access to BMD. For low-risk patients, insured BMD testing is available no more frequently than once every 24 months.

Adapted from Josse et al.[3]

intravenous or subcutaneous heparin therapy—including low molecular weight heparin—thyroxine, gonadotropin-releasing hormone agonists, and others) and diseases (hyperthyroidism, rheumatoid arthritis, hyperparathyroidism, malabsorption, hyperprolactinemia, immobilization, and others) associated with greater risk of decreased bone mass.

At this date, dual energy x-ray absorptiometry (DXA) is preferred for measuring BMD.[3] Nearly all data on fracture risk and efficacy of therapy are based on DXA measurements of BMD of the hip and lumbar spine. Other technologies and sites of measurement of BMD (wrist, heel) are under evaluation, are providing useful information, and are preferable to no measurement of BMD in assigning risk and influencing treatment decisions.

No other technology or sites, however, have been evaluated as comprehensively as DXA measurements of hip and lumbar spine BMD. The precision of DXA measurements of the spine (about 1% to 2%) and hip (about 3%) is very good. Based on this precision of measurement and the usual rate of bone loss in untreated postmenopausal women (around 2% yearly), screening untreated, uncomplicated patients more frequently than every 2 years is unlikely to reveal meaningful changes.

Among patients receiving therapy, BMD monitoring can be useful for assessing response. Yet based on the magnitude of response to current therapies, meaningful increases in BMD (eg, 3% or more at the spine and 6% or more at the hip) are unlikely to be detected earlier than after 2 years of therapy. Nevertheless, measurement after a year of therapy could be useful for identifying patients who have lost more bone than expected.[3,4] These patients require reevaluation of therapy, particularly to see whether they comply with the full therapeutic regimen.

Patients with diseases such as hyperparathyroidism or who receive drugs associated with enhanced bone loss could also benefit from more frequent evaluations of BMD. For example, patients on long-term steroid treatment should have a baseline measurement. For those not receiving antiosteoporosis therapy, BMD measurement should be repeated in 6 months to reevaluate need for treatment because bone loss can be very rapid and account for as much as a 17% decrease of the skeleton in the first 6 to 12 months of steroid therapy.[4] For those taking antiosteoporosis drugs, a repeat BMD in 1 year is indicated to assess the effectiveness of the therapy.

There are some recent caveats about the utility of monitoring BMD in patients receiving therapy. First, BMD measurements currently are not standardized among centres. Centres use machines bought from various manufacturers to test various control groups. Because precision of BMD measurement is crucial for making therapeutic decisions, diagnosis and monitoring of patients should be restricted to one centre. Attention to quality control at a centre should allow comparison of results from BMD measurements performed over time. Second, the desired end point of therapeutic intervention is reduced incidence of new osteoporotic fractures.

Just as a decreased BMD measurement has been accepted as a surrogate marker for increased fracture risk, increased BMD has been accepted as a

surrogate marker for reduced fracture incidence. This is supported by the results of the Fracture Intervention Trial[16] evaluating the benefits of alendronate. The reduction in risk for new vertebral fractures increased progressively with the magnitude of increase in BMD.[16] Results of other studies with such therapies as vitamin D and calcium, nasal calcitonin, and raloxifene, however, clearly show that substantial reductions in fracture incidence can occur with more modest changes in BMD.[14] These data indicate that some drugs can enhance the integrity of bone, probably via a reduction in bone turnover, and that the improved quality of bone helps to reduce fractures without large increases in bone mass. These data do not negate the value of monitoring changes during therapy because monitoring is intended to identify patients experiencing increasing bone loss despite therapy.

Secondary causes of osteoporosis

In general, most cases of osteoporosis can be explained by age, withdrawal of sex hormones, and use of medications (particularly corticosteroids). The amount of bone an adult has at a particular age is determined by achievement of peak bone mass at about age 30 and by subsequent rate and duration of bone loss. Men acquire around 30% more peak bone mass than women, and white women have about 8% less bone than black women.[17] Genetic and lifestyle factors (**Table 1**[3]) are important determinants of peak bone mass. Genetic factors, especially heterogeneity in gastrointestinal receptors for vitamin D, could account for most of the variation in BMD among young women,[18] and similar factors might ultimately also be identified among men. Lifestyle choices also substantially modify peak bone mass, particularly among women, by diminishing gonadal function or nutrient intake (anorexia, excessive exercise, dieting, smoking, and drinking).

Following acquisition of peak bone mass, there is a gradual (about 1%) decline yearly in both men and women. During the first 5 to 10 years after menopause, the rate of loss in women can accelerate to 2% to 4% yearly.[19] During an average lifetime, hip bone density declines about 50% among women and 30% among men.[4]

As most cases of osteoporosis have many causes, classification of osteoporosis into primary and secondary categories is somewhat of an oversimplification. Still, secondary causes of osteoporosis should be considered when a low BMD measurement cannot be readily explained by the usual risk factors (**Table 1**). It must be kept in mind that the risk factors outlined in **Table 1** are derived from studies of white women. Less is known about the epidemiology of osteoporosis in women of other races and in men. Secondary causes of osteoporosis[20] are outlined in **Table 4.**[20] Note the overlap between conditions listed in **Tables 3** and **4** as well as the rarity of some of the conditions listed in **Table 4**.

In men, a substantial proportion of cases of osteoporosis are secondary to hypogonadism. Causes of hypogonadism include primary testicular failure,

Table 4. Causes of secondary osteoporosis

ENDOCRINE
Male hypogonadism
Hyperthyroidism
Hyperparathyroidism
Hypercortisolism
Diabetes
Homocystinuria
AMENORRHEA
Amenorrheic athletes
Anorexia nervosa
Hyperprolactinemia
DRUGS
Anticonvulsants
Thyroxine
Heparin
Steroids
Chemotherapy
NEOPLASIA
Multiple myeloma
Skeletal metastases (eg, breast, thyroid, lung, prostate, renal cell)
OTHERS
Transplantation
Gastrointestinal (eg, gastric surgery, malabsorption, celiac disease)
Alcoholism
Immobilization
Osteogenesis imperfecta
Systemic mastocytosis
Pregnancy

Adapted from Anderson and Francis.[21]

Klinefelter syndrome, idiopathic hypogonadotropic hypogonadism, hyperprolactinemia, and hemachromatosis. Measurement of serum testosterone and gonadotropins should be part of the routine evaluation of ascertaining the cause of osteoporosis in men. Alcoholism is another factor implicated in causing hypogonadism in men, although most male alcoholics have normal testosterone levels and osteoporosis can be blamed on the diverse effects of alcohol on bone formation. Alcoholism should always be suspected when osteoporosis affects men.

In addition to endogenous hyperthyroidism causing osteoporosis, exogenous thyroxine administration can also reduce bone density, even though a patient is biochemically euthyroid. Bone loss is most marked in the first 6 months of therapy. Methotrexate, even at the relatively small doses used to treat rheumatoid arthritis and psoriasis, can cause osteoporosis.

A malignancy must always be considered among the possible causes of osteoporosis and fractures in any patient. Multiple myeloma can cause diffuse osteoporosis. Other tumours are more likely to cause osteolytic (thyroid, kidney, bowel, breast) or osteoblastic (prostate, breast, Hodgkin's lymphoma) metastases. Workup of patients with severe bone pain, fractures, and osteoporosis is directed in part toward diagnosing underlying malignancy (**Table 5**). Investigations to complement those in **Table 5** will be directed also by the clinical situation and results of initial screening.

Table 5. Investigations for secondary causes of osteoporosis

Full physical examination (thyroid, breast, and prostate gland evaluation): rule out tumour metastases to bone
Complete blood count, erythrocyte sedimentation rate, serum and urine protein electrophoresis: rule out multiple myeloma
Blood urea nitrogen and creatinine: rule out renal disease
Liver function tests: rule out liver disease
Serum thyroid-stimulating hormone: rule out hyperthyroidism
Calcium, phosphate, alkaline phosphatase, parathyroid hormone: rule out hyperparathyroidism
Prostate-specific antigen: rule out prostate metastases
Testosterone, follicle-stimulating hormone, and luteinizing hormone (in men): rule out hypogonadism

Conclusion

Much remains to be said for preventing osteoporosis by following a proper diet (proper intake of calcium and vitamin D), exercising, and avoiding smoking and alcohol. These are useful, nonmedicinal approaches with relevance for women and men of all ages. Still, despite all the best lifestyle adjustments, a large portion of the population will develop osteoporosis because of hormone withdrawal, age, and drugs or diseases that promote bone loss. The advent of bone densitometry has revolutionized diagnosis and management of osteoporosis. It is simply the best objective predictor of fracture risk.

The relatively high cost of obtaining BMD measurement has tempered its use as a general screening test; this could change when future costs diminish. Even at low cost, however, indiscriminate screening cannot be advocated. Measurement of any risk factor is clinically relevant only if the information will be used to make therapeutic decisions. The recommendations of the OSC and similar groups worldwide recognize the high prevalence and costs of osteoporosis in our aging population and provide the impetus to pursue earlier diagnosis and therapy.

Editor's key points

- Bone mineral density (BMD) measurement by dual energy x-ray absorptiometry is preferred for evaluating risk of osteoporosis and fracture.
- Given the high human and financial cost and the insidious nature of osteoporosis, selected screening of at-risk groups is recommended.
- Dual energy x-ray absorptiometry is also useful for monitoring patients treated for osteoporosis or patients receiving risk-enhancing medications, such as steroids or low-molecular-weight heparin.

Points de repère du rédacteur

- La mesure du contenu minéral osseux (CMO) au moyen de l'absorptiométrie à rayons X en double énergie constitue l'intervention privilégiée pour évaluer les risques d'ostéoporose et de fracture.
- Compte tenu des coûts sur le plan humain et financier et de la nature insidieuse de l'ostéoporose, il est recommandé de procéder à un dépistage ciblé des groupes à risque élevé.
- L'absorptiométrie à rayons X en double énergie est également utile pour exercer la surveillance des patients traités pour l'ostéoporose ou de ceux qui prennent des médicaments qui accroissent le risque d'en souffrir, comme les stéroïdes ou l'héparine de faible masse moléculaire.

Competing interests

None declared

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